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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,316	08/22/2001	Ching-Leou Teng	ISIS-4824	1463

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,316	TENG ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 1/3/2006 is acknowledged. The amendment has been entered. Claims 30-40 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 30-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/60012 (TENG et al. cited by Applicants in the IDS filed 8/18/2003) in view of U.S. Patent 5,672,359 (DIGENIS et al.) and further in view of MURANISHI (Critical Reviews in Therapeutic Drug Carrier Systems; 1990 Vol. 7, pages 1-33) for the reasons of record set forth in the Office Action mailed 9/7/2005.

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/60012 (TENG et al. cited by Applicants in the IDS filed 8/18/2003) in view of U.S. Patent 4,773,907 (Urquhart et al.) and further in view of MURANISHI (Critical Reviews in Therapeutic Drug Carrier Systems; 1990 Vol. 7, pages 1-33).

The instant claim is drawn to:

A method for enhancing the intestinal absorption of a drug in an animal, said method comprising administering to the animal:

(a) a first population of carrier particles comprising a drug-bioadhesive component; and,

(b) a second population of carrier particles comprising a penetration enhancer,

wherein intestinal tissue is activated by said penetration enhancer prior to the arrival of said drug and said first population and second population of carrier particles are administered in a single pharmaceutical formulation and wherein the first population and second population of particles are released concurrently to said intestinal tissue.

WO 99/60012 (TENG et al.) teaches a composition and method for enhancing the intestinal absorption of an oligonucleotide in an animal wherein the composition comprises a penetration enhancer such as a bile salt, fatty acid, or chelating agent (e.g., see page 3 lines 33-37) as well as other carriers or excipients including hydroxypropyl methylcellulose (HPMC) gelatin, polyacrylates, and starch (e.g., see page 18, lines 4-25; page 54, lines 22-35). WO 99/60012 teaches a working example wherein an oral dosage comprising an oligonucleotide (ISIS-2302), a penetration enhancer(s) and an excipient is administered to an animal (e.g., see Example 15, pages 95-100). WO 99/60012 also teaches that the composition can be formulated into a tablet or capsule for oral administration wherein the tablet is constructed to provide for slow or controlled release of the active ingredients (e.g., see page 53, lines 1-23).

WO 99/60012 does not explicitly teach that the drug (i.e., the oligonucleotide) is comprised in a first population of carrier particles with a bioadhesive and that the penetration

enhancer is comprised in a second population of carrier particles wherein the first and second population are comprised in a single dosage form wherein the two populations are released concurrently such that the penetration enhancer activates the intestinal epithelium prior to arrival of the drug/bioadhesive.

Urquhart et al. teach a delivery system for delivering a pharmaceutical agent or agents to the gastrointestinal tract of an animal (e.g., see column 1, lines 15-31). Specifically, Urquhart et al. teach a delivery system comprising an exterior wall that surrounds a lumen housing a plurality of dispensable dosage forms wherein the exterior wall is formed of an environment sensitive material that releases the dosage forms into the environment. The dosage forms comprise a wall that surrounds a compartment containing a drug with a passageway in the wall for delivering the drug overtime. The dosage form is useful for delivering a single drug, two drugs or more, that are separately housed and separately dispensed for (a) obtaining the therapeutic benefits of each drug, (b) lessening the incidence of adverse effects due to the incompatibility of different drugs, (c) delivering at least two drugs that are difficult to deliver from a dispensing system, or (d) dispersing a drug in a preselected area of the gastrointestinal tract (e.g., see column 1, lines 15-31). Urquhart also specifically teaches that the delivery system can be used for "housing a drug, or two, or more different drugs for independent or for simultaneous independent co-delivery at continuous and controlled rates in therapeutically effective amounts for obtaining the benefits of each drug..." (see column 2, lines 55-65).

Furthermore, the use of penetration enhancers (also known as absorption enhancers) to facilitate the absorption of drugs into intestinal epithelium was well known in the art (e.g., see Muranishi). Specifically Muranishi teaches that many drugs are impermeable to outer tissue

barriers and that delivery of the impermeable drugs through such barriers is one of the major interests in pharmaceutical research. Muranishi teaches that a number of absorption enhancers provide rapid absorption in the gastrointestinal tract or the skin (e.g., see abstract; page 27; etc.). Specifically, Muranishi reviews several absorption enhancers (including bile salts and fatty acids) which are capable of enhancing intestinal drug delivery by increasing the permeability of intestinal epithelium (e.g., see page 11-19). Therefore, one of skill in the art would have recognized that in order to increase the permeability of the intestinal epithelium, the absorption enhancer should reach the target tissue either prior to or concurrently with the arrival of the drug.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use a formulation comprising the delivery system taught by Urquhart et al. such that the system is a capsule comprising separate dosage forms wherein one dosage form is a penetration enhancer such as a bile salt, fatty acid, or chelating agent (as taught by TENG) and another dosage form is a drug (e.g., an oligonucleotide) and a carrier/excipient such as a polyacrylic polymer, HPMC and/or starch (as taught by TENG) wherein the delivery system delivers the two dosage forms are delivered by simultaneous independent co-delivery (i.e., concurrent delivery) with a reasonable expectation of success. It is noted that polyacrylic polymers, HPMC and starch are "bioadhesive" agents as disclosed in the instant specification.

The motivation to combine the references to create claimed invention is provided by WO 99/60012 (TENG et al.) who teaches a method of enhanced delivery of an drug to intestinal tissue using a composition comprising a penetration enhancer, a drug (e.g., oligonucleotide) and various excipients (e.g., HPMC) and specifically indicates that a controlled release delivery

system can be used as a controlled release capsule for delivering the oligonucleotide to the intestine of an animal.

Response to Arguments

Applicant's arguments filed 1/3/2005 have been fully considered by the Examiner but are not persuasive. Applicants argue that the multilayer capsule taught by Digenis is distinct from the instant invention which that teaches a first and second carrier particle composition wherein the first population comprises a drug-bioadhesive and the second population comprises a penetration enhancer. Applicants assert that the combination of the drug with the bioadhesive into carrier particles rather than with the penetration enhancer with the bioadhesive, or as a homogenous mixture is an essential aspect of the instant invention. Applicants contend that the instant invention allows for the tissue to be activated by the penetration enhancer prior to the arrival of the drug as it transits through the maximum area of activated tissue. Applicants assert that this arrangement of components is clearly stated in the claims which require the combination of drug and bioadhesive in a population of particles. Applicants assert that having two separate populations of particles allows for the penetration of an oral dosage formulation "in a manner that does not impair the adhesive or release properties of the other" population of particles as discussed in paragraph 0017. Applicants argue that this is clearly distinct from Digenis who teaches a hard capsule and which comprises a three compartment delivery system for its pharmacologically active components. Applicants argue that the hydroxypropyl methylcellulose (HPMC) forms the hard outer capsule therefore it would not be formed into formed into particles or commingled with the drug as claimed.

In response, it is respectfully pointed out that TENG teaches a method of delivering a drug (specifically an oligonucleotide) by administering a composition comprising a penetration enhancer, the drug as well as other carriers or excipients such as HPMC, gelatin, starch, etc. It is noted that the instant specification discloses as number of "bioadhesive" agents including: HPMC, gelatin and starch. Therefore, TENG teaches a method of delivering a drug to a subject by administering a composition comprising a penetration enhancer such as a fatty acid, a drug such as an antisense oligonucleotide and another "bioadhesive" agent such as HPMC. TENG does not explicitly teach that the penetration enhancer is in one population of particles and that the drug/bioadhesive are in a second population of particles; however, TENG teaches that the composition can be delivered using a multicompartment capsule such as the one specifically taught by Digenis. Therefore, the only aspects of the claimed invention that TENG does not teach is that the penetration enhancer and the drug-bioadhesive are two separate populations of particles and that the penetration enhancer activates the intestinal epithelium prior to arrival of the oligonucleotide-bioadhesive. However, it would have been prima facie obvious to use the capsule taught by Digenis (as explicitly suggested by TENG) wherein one compartment of the capsule comprised the penetration enhancer particles and the another compartment comprised the oligonucleotide with HPMC/gelatin/starch or any other excipient/carrier taught by TENG such that oligonucleotide/carrier particles were a second population of particles. Furthermore, one of ordinary skill in the art would know to construct the capsule such that the penetration enhancer particles were released prior to the oligonucleotide/bioadhesive particles based on Muranishi who teaches that absorption enhancers such as fatty acids or bile salts enhance intestinal drug delivery by increasing the permeability of the intestinal epithelium. Therefore, although the

capsule taught by Digenis might be distinct from the instant invention, it would have been prima facie obvious to use the capsule taught by Digenis to deliver the penetration enhancer particles as well as the oligonucleotide taught by TENG wherein the oligonucleotide is administered with a carrier/excipient such as a fatty acid or bile salts which are "bioadhesive" agents. It is noted that using the capsule taught by Digenis wherein one compartment of the capsule comprises the penetration enhancer which is released prior to the oligonucleotide and carrier (i.e., drug-bioadhesive) would allow for the intestinal epithelium to be activated by the penetration enhancer prior to the arrival of the drug as it transits through the activated intestine. Furthermore, the compartments of the capsule would comprise penetration enhancer particles and drug-bioadhesive particles as suggested by TENG. Furthermore, using the capsule taught by Digenis to deliver the penetration enhancer and the drug with a carrier taught by TENG would allow for the release of the contents of one compartment such that it would not impair the adhesive or release properties of the contents of the other compartment. Furthermore, it is irrelevant if Digenis teaches that HPMC makes up the hard component of the capsule as the instant rejection does not rely on the HPMC of Digenis as the "bioadhesive" agent. Rather, the instant rejection merely relies on the capsule of Digenis to deliver the components taught by TENG which are the penetration enhancer, the drug and "bioadhesive" agent (e.g., HPMC, bile salts, fatty acids etc.). Furthermore, the penetration enhancer and drug/bioadhesive taught by TENG would be particles (i.e., particulate in nature) and not part of the hard capsule. Therefore, Applicants arguments are not persuasive.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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